Research Article

Hydrogel Catalyst for A Simple Synthesis of pyrano[3,2-c]pyridines derivatives

H. Fathinejad Jirandehi*
Department of Chemistry, Farahan Branch, Islamic Azad University, Farahan, Iran.
***Corresponding author's E-mail:** hfathinejad@iau-farahan.ac.ir

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ABSTRACT

Synthesis of pyrano[3,2-c]pyridines derivatives carried out via cyclocondensation of aryl aldehydes, malononitrile and ethylacetoacetate with basic hydrogel catalyst in H_2O/ethanol solvent in reflux conditions. Then, the solution was separated by filtration and removed of solvent by vacuum condition. The crud products were recrystallized by ethanol. All compounds were confirmed by FT-IR and ^1H, ^{13}C NMR.

Keywords: Hydrogel, cyclocondensation, pyrano[3,2-c]Pyridines, reversible catalyst.

INTRODUCTION

Pyranopyridines are an important group of heterocyclic compounds with biological activities such as antimycobacterial[1], Inhibitor of the AcrAB Efflux Pump of *Escherichia coli*[2], and estrogenic. Among the different substitution patterns that are known, benzopyrano[2,3-*b*]pyridines exhibit anti-proliferative, cancer chemopreventive[3]. Pyranopyridines are chemically interesting molecules due to their structural similarity to quinolines, substituted pyridines, and benzopyranes and are important intermediates in the synthesis of biologically active compounds.

More methods for the preparation of pyranopyridines needed high reaction temperature or highly functionalized pyridine derivatives which cannot be easily prepared[4]. In other researchs, synthesis of pyanopridines using LiCl Mediated palladium.[5]

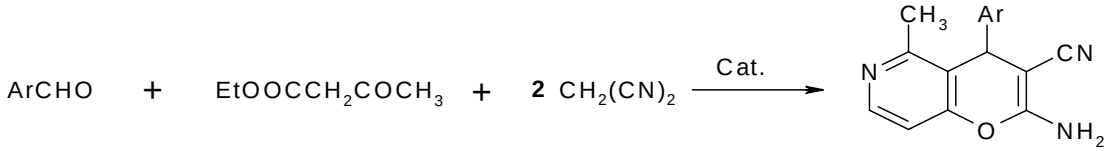
Synthesis of novel pyranopyridine derivatives involving chromenes were done under controlled microwave irradiation[3]. Recently, we reported synthesis of pyrano[3,2-c]Pyridines derivative using piperazine catalyst in medium condition.[6]

Super absorbent polymers are a unique group of polymeric materials which absorb great amounts of water when left in a water medium for long times. Biocompatible and biodegradable hydrogels have a wide application in the field of hygienic products[7], agriculture[8], drug delivery systems[8, 9], sealing[7], as a reusable heterogeneous catalyst for the direct aldol reaction[10] and Highly efficient and reusable hydrogel-supported nano-palladium catalyst for Evaluation for Suzuki–Miyaura reaction in water[11].

In this work, a simple three-component reaction reported four organic components react to form pyranopyridines compounds by basic properties of the hydogel as catalyst with easy separate able in filtration step.

2-amino-5-methyl-4-aryl- -4H-pyrano [3, 2-c] pyridine-3-carbonitrile (4) as final product was prepared by reaction between malononitrile (1), ethyl acetoacetate (2) and benzaldehyde (3) in the presence of a mediated catalyst, which consists of 5-10% of a base with piperazine, as shown in Figure 1.

Figure 1



1 2 3 4

MATERIALS AND METHODS

All chemicals (ketoester, arylaldehyde, malononitrile were purschad from MERCK and Fluka as reagent grade quality and used without further purification. Melting points were determined on an electrothermal digital melting point apparatus. ^1H, ^{13}C NMR spectra were recorded on a Brucker 300 MHz spectrometer. IR spectra were performed on a Galaxy FT-IR 500 spectrophotometer.

Preparation of basic hydrogel

Ammonium persulfate and N,N,-methylene bis acrylamide and acrylic acid added to solution. The solution stirred for 15 min and then system keep in heating for 20 min to be completed gel formation process. Then, basic hydrogel

was prepared by adding of hydrogel to NaOH solution for formation of salt of carboxylic acid groups. The formed gel washed by distilled water at room temperature and dried in oven at 50 °C for 24 h.

General Producer for pyranopyridines

A mixture of ethyl acetoacetate (1 mmol), aldehyde (2.2 mmol), malononitrile (4 mmol) and 0.1 g basic hydrogel powder mixed in a reflux system. Then, the mixture was heated in boiling temperature for 10 h. the mixture was cooled in the room temperature, filtered for separation of swelled hydorgel from solution. The crud products were prepared via solvent removed by vacuum condition. Then, the precipitated solids were purified by ethanol.

2-amino-5-methyl-4-(2,5-dimethoxyphenyl)-4H-pyrano [3, 2-c] pyridine-3-carbonitrile (4a). mp. 222-225 ° C IR (KBr): 3391(NH_2), 3209(NH_2), 3067(CH_{arom}), 2980(CH_{aliph}), 2202(CN), 1626 cm^{-1}.

^{1}H NMR (300 MHZ, DMSO-d_6): δ 8.61 (bs, 1H), 7.40(d, 1H), 7.11(d, 1H), 7.01(d, 1H), 6.94 (m, 1H), 5.88 (s, 1H), 3.74(d, 6H), 3.14(s, 3H).

^{13}C NMR (300 MHZ, DMSO-d_6): δ 162(C=C), 159(C=C), 151(C=C), 130(C=C),129,122(C=C), 120(C=C), 117 (C=C), 106(C=C), 100(C=C), 98(C=C), 78(CN), 55(OCH_3), 35(CH), 23(CH_3).

2-amino-5-methyl-4-(2, 4-dimethoxyphenyl)-4H-pyrano [3, 2-c] pyridine-3-carbonitrile (4b). mp. 236-239 ° C

IR (KBr): 3344(NH_2), 3212(NH_2), 3051(CH_{arom}), 2937(CH_{aliph}), 2202(CN), 1626 cm^{-1}.

^{1}H NMR (300 MHZ, DMSO-d_6): δ 8.73 (bs, 1H), 7.37-7.50(m, 2H), 7.03(d, 1H), 6.60(d, 1H), 5.85 (s, 1H), 3.86(d, 6H), 3.27(s, 3H).

^{13} C NMR (300 MHZ, DMSO-d_6): δ 162(C=C), 158(C=C), 151(C=C),135(C=C),129(C=C), 127(C=C), 120(C=C),117 (C=C), 101(C=C), 79(CN), 57(OCH_3), 38(CH), 20(CH_3).

2-amino-5-methyl-4-(4-hydroxyphenyl)-4H-pyrano [3, 2c] pyridine-3-carbonitrile (4c). mp. 250-253 ° C

IR (KBr): 3443(OH),3344(NH_2), 3194(NH_2), 3043(CH_{arom}), 2990(CH_{aliph}), 2214(CN), 1716(C=C),1606(C=C) cm^{-1}.

^{1}H NMR (300 MHZ, DMSO-d_6): δ 8.61 (bs, 1H), 7.40(d, 1H), 7.11(d, 1H), 7.01(d, 1H), 6.94 (m, 1H), 5.88 (s, 1H), 3.74(d, 6H), 3.14(s, 3H).

^{13}C NMR (300 MHZ, DMSO-d_6): δ 162(C=C), 159(C=C), 155(C=C), 150(C=C), 135(C=C), 129(C=C), 127(C=C), 120(C=C), 117 (C=C), 101(C=C), 79(CN), 35(CH), 21(CH_3).

2-amino-5-methyl -4-(4-methylphenyl)-4H-pyrano [3, 2-c] pyridine-3-carbonitrile (4d). mp. 230-232°C

IR (KBr): 3391(NH_2), 3209(NH_2), 3067(CH_{arom}), 2980(CH_{aliph}), 2202(CN), 1626 cm^{-1}.

^{1}H NMR (300 MHZ, DMSO-d_6): δ 8.59 (bs, 1H), 7.43(d, 1H), 7.11-7.14(m, 5H), 4.84 (s, 1H), 2.53(s, 3H), 2.34(s, 3H).

^{13}C NMR (300 MHZ, DMSO-d_6): δ 166(C=C), 157(C=C), 153(C=C), 145(C=C),133,130(C=C), 128(C=C), 126 (C=C), 120(C=C), 118(CN), 108(C=C), 78(C=C), 34(CH), 21(CH_3), 19(CH_3).

2-amino-5-methyl -4-(4-fluorophenyl)-4H-pyrano [3, 2-c] pyridine-3-carbonitrile (4e). mp. 239-241°C

IR (KBr): 3381(NH_2), 3214(NH_2), 3053(CH_{arom}), 2986(CH_{aliph}), 2212(CN), 1626 cm^{-1}.

^{1}H NMR (300 MHZ, DMSO-d_6): δ 8.57 (bs, 1H), 7.38(d, 1H), 7.21(d, 2H), 7.14(d, 1H), 7.12(d, 2H), 5.85 (s, 1H), 2.54(s, 3H).

^{13}C NMR (300 MHZ, DMSO-d_6): δ 164(C=C), 158(C=C), 152(C=C), 143(C=C),132,130(C=C), 127(C=C), 125 (C=C), 121(C=C), 117(CN), 105(C=C), 76(C=C), 32(CH), 19(CH_3).

2-amino-5-methyl -4-(4-chlorophenyl)-4H-pyrano [3, 2-c] pyridine-3-carbonitrile (4f). mp. 242-245°C

IR (KBr): 3390(NH_2), 3204(NH_2), 3101(CH_{arom}), 2991(CH_{aliph}), 2214(CN), 1636 cm^{-1}.

^{1}H NMR (300 MHZ, DMSO-d_6): δ 8.59 (bs, 1H), 7.42(d, 1H), 7.33(d, 2H), 7.18(d, 2H), 7.12(d, 1H), 5.81(s, 1H), 2.58(s, 3H).

δ 162(C=C),158(C=C),151(C=C), 141(C=C),134,130(C=C), 128(C=C), 124 (C=C), 120(C=C), 118(CN), 106(C=C), 77(C=C), 31(CH), 20(CH_3).

2-amino-5-methyl -4-(2-chloro-4-fluorophenyl)-4H-pyrano [3, 2-c] pyridine-3-carbonitrile (4g). mp. 235-238°C

IR (KBr): 3391(NH_2), 3209(NH_2), 3067(CH_{arom}), 2980(CH_{aliph}), 2202(CN), 1626 cm^{-1}.

^{1}H NMR (300 MHZ, DMSO-d_6): δ 8.60 (bs, 1H), 7.70(d, 1H), 7.41(d, 1H), 7.14-7.17 (m, 2H), 6.94 (m, 1H), 5.78 (s, 1H), 2.58(s, 3H).

^{13} C NMR (300 MHZ, DMSO-d_6): δ 164(C=C), 157(C=C), 153(C=C), 150(C=C), 131(C=C), 129(C=C), 122(C=C), 120(C=C), 117 (CN), 108(C=C), 102(C=C), 96(C=C), 77(C=C), 33(CH), 23(CH_3).

2-amino-5-methyl -4-phenyl-4H-pyrano [3, 2-c] pyridine-3-carbonitrile (4h). mp. 216-219 ° C

IR (KBr): 3385(NH_2), 3212(NH_2), 3056(CH_{arom}), 2985(CH_{aliph}), 2209(CN), 1636 cm^{-1}.

^{1}H NMR (300 MHZ, DMSO-d_6): δ 8.62 (bs, 1H), 7.42(d, 1H), 7.20-7.28(m, 5H), 6.94 (d, 1H), 5.83 (s, 1H), 3.12(s, 3H).

^{13} C NMR (300 MHZ, DMSO-d_6): δ 162(C=C), 159(C=C), 151(C=C), 138(C=C),135(C=C),132(C=C), 129(C=C), 117 (CN), 106(C=C), 101(C=C), 78(C=C), 35(CH), 19(CH_3).

2-amino-5-methyl -4-(4-nitrophenyl)-4H-pyrano [3, 2-c] pyridine-3-carbonitrile (4i). mp. 248-250 ° C

IR (KBr): 3371(NH_2), 3194(NH_2), 3127(CH_{arom}), 2990(CH_{aliph}), 2212(CN), 1646 cm^{-1}.

^{1}H NMR (300 MHZ, DMSO-d_6): δ 8.63 (bs, 1H), 8.14(d, 2H), 7.49(d, 2H), 7.40(d, 1H), 7.14 (m, 1H), 5.74 (s, 1H), 3.3(s, 3H).

^{13}C NMR (300 MHZ, DMSO-d_6): δ 162(C=C), 157(C=C), 154(C=C), 144(C=C), 129(C=C), 123(C=C), 120(C=C), 117 (CN), 106(C=C), 100(C=C), 98(C=C), 78(C=C), 28(CH), 19(CH_3).

2-amino-5-methyl -4-(2 -methylphenyl)-4H-pyrano [3, 2-c] pyridine-3-carbonitrile (4j). mp. 222-225 ° C

IR (KBr): 3391(NH_2), 3209(NH_2), 3067(CH_{arom}), 2980(CH_{aliph}), 2202(CN), 1626 cm^{-1}.

^{1}H NMR (300 MHZ, DMSO-d_6): δ 8.59 (bs, 1H), 7.40(d, 1H), 7.34(d,1H), 7.14(m, 3H), 7.11(d, 1H), 5.78 (s, 1H), 2.57(s, 3H).

^{13}C NMR (300 MHZ, DMSO-d_6): δ 161(C=C), 158(C=C), 147(C=C), 38(C=C),136(C=C),130(C=C),125(C=C),124(C=C), 119(C=C), 118 (CN), 107(C=C), 100(C=C), 78(C=C), 33(CH), 21(CH_3), 19(CH_3).

2-amino-5-methyl -4-(2-thionyl)-4H-pyrano [3, 2-c] pyridine-3-carbonitrile (4k). mp. 222-225 ° C

IR (KBr): 3375(NH_2), 3218(NH_2), 3112(CH_{arom}),, 3105(CH_{arom}), 2979(CH_{aliph}), 2210(CN), 1636 cm^{-1}.

^{1}H NMR (300 MHZ, DMSO-d_6): δ 8.53 (bs, 1H), 7.48(d, 1H), 7.42(d, 1H), 7.11(d, 1H), 6.93(d, 1H), 6.83 (m, 1H), 5.74 (s, 1H), 2.6(s, 3H).

^{13}C NMR (300 MHZ, DMSO-d_6): δ 162(C=C), 160(C=C), 155(C=C), 127(C=C), 126(C=C), 125(C=C), 120(C=C), 117 (CN), 106(C=C), 68(C=C), 29(CH), 20(CH_3).

2-amino-5-methyl -4-(2-nitrophenyl)-4H-pyrano [3, 2-c] pyridine-3-carbonitrile (4l). mp. 247-255°C

IR (KBr): 3391(NH_2), 3209(NH_2), 3067(CH_{arom}), 2980(CH_{aliph}), 2202(CN), 1626 cm^{-1}.

^{1}H NMR (300 MHZ, DMSO-d_6): δ 8.63 (bs, 1H), 7.96(d,1H), 7.44(d, 1H), 7.52(d, 1H), 7.49(d, 1H), 7.14 (d, 1H), 5.91 (s, 1H), 2.53(s, 3H).

^{13}C NMR (300 MHZ, DMSO-d_6): δ 162(C=C), 159(C=C), 155,(C=C), 149(C=C), 134(C=C), 130(C=C),128(C=C), 126(C=C), 124, 122(C=C), 120(C=C), 116 (CN), 106(C=C), 75(C=C), 24(CH), 18(CH_3).

2-amino-5-methyl -4-(3, 4-dimethoxyphenyl)-4H-pyrano [3, 2-c] pyridine-3-carbonitrile (4m), mp. 224-226 ° C

IR (KBr): 3378(NH_2), 3234(NH_2), 3054(CH_{arom}), 2988(CH_{aliph}), 2205(CN), 1636 cm^{-1}.

^{1}H NMR (300 MHZ, DMSO-d_6): δ 8.63 (bs, 1H), 7.43(d, 1H), 7.23(d, 1H), 6.99(d, 1H), 6.91(d, 1H), 6.72 (m, 1H), 5.87 (s, 1H), 3.84(d, 6H), 2.59(s, 3H).

^{13}C NMR (300 MHZ, DMSO-d_6): δ 162(C=C), 159(C=C), 151(C=C), 149(C=C), 146(C=C), 128(C=C),122(C=C), 120(C=C), 118 (CN), 108(C=C), 102(C=C), 75(C=C), 55(OCH_3), 35(CH), 23(CH_3).

RESULTS AND DISCUSSION

To finding of simple procedure of synthetic, study done on catalyst properties for optimizing of the reaction conditions. The reaction of benzaldehyde, malononitrile and ethylactetoacetate was investigated in different condition such as molar ratio, temperature, solvent. The presence of basic hydrogel in reaction mixture shown that cyclocondensation of of benzaldyhe to ethylacetoacetate and malononitrile was done with molar ratio equal to 1:1:2 in reflux condition of solvent.

The reactions proceeded to completion almost instantaneously, and the pure product was obtained by a simple purification using an acidic aqueous solution (HCl 0.1 N), without using any chromatographic techniques. The products obtained from reaction between malononitrile, ethyl acetoacetate and other aromatic components are showed in Table 1. The maximum yield of 94% was obtained for the product 4b. All the synthesized compounds were characterized by IR, ^{1}H and ^{13}C NMR.

CONCLUSION

Synthesis of several some derivatives 4a-4m by the direct cyclocondensation reaction of maleonitrile (3) with aldehyde (1) and ethylaceoacetate (2) by using a hydrogel based catalyst and reflux condition. The reversible nature of hydrogel system allows for easy recovery and regeneration of the catalyst.

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